# Whipple's disease? A case report and discussion

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## Abstract

**Background.** Whipple's disease (WD) is a rare chronic systemic disease caused by the Gram-positive bacillus Tropheryma whipplei. Despite over 100 years of observation and study history of this disease, it still remains a difficult diagnostic and therapeutic challenge.

**Clinical case presentation.** Authors report the case of a 38-year-old man with long-time PPIs treatment because of GERD and no other clinical and paraclinical symptoms. Endoscopic slightly enlarged villi, accumulation of whitish matter at the tip of the villi of distal duodenal mucosa and periodic acid-Schiff staining positive inclusions in the stromal tissue may be typical signs of Whipple's disease. In discussion the possible explication of this case are presented.

**Conclusions.** It is still a challenge to diagnose Whipple's disease. Histological findings may confirm the diagnosis in patients with a combination of typical clinical manifestations, but histological signs alone are not pathognomic, and are not enough for a definitive diagnosis.

**Keywords:** Whipple's disease diagnosis, PAS positive inclusions

## Introduction

Whipple's disease (WD) is a rare chronic systemic disease caused by the Gram-positive bacillus Tropheryma whipplei [1]. Despite over 100 years of observation and study history of this disease, it still remains a difficult diagnostic and therapeutic challenge. The majority of the described Whipple disease cases involve severe disorders with multiple, polyorganic affectations and a progressive evolution [2-5].

## Clinical case

We present a case of patient without clinical symptoms but with typical endoscopic and histological modifications. A 38-year-old man had a history of gastroesophageal reflux disease since 2016 with varying degrees of esophagitis at different moments of the disease. The patient had no other digestive or other disorders. He had been taking double doses of PPIs for a long period to control the disease. The general physical condition was good, no clinically significant abnormalities in objective and common laboratory data. In March 2018, a planned upper gastrointestinal endoscopy was performed. Endoscopic examination confirmed GERD with low esophageal sphincter insufficiency, reflux esophagitis gr. A, and, unexpectedly, slightly enlarged villi with an accumulation of whitish matter at the tip of the villi of distal duodenal mucosa were observed for the first time (Figure 1).

Histological examination observed moderate lympho-plasmocytes infiltrate in *lamina propria* and foamy macrophage cells with pale and finely granulated cytoplasm, with PAS-positive inclusions in the stromal tissue (Figure 2). These findings may be typical signs of WD [1,5,6].

DOI: 10.15386/mpr-2237

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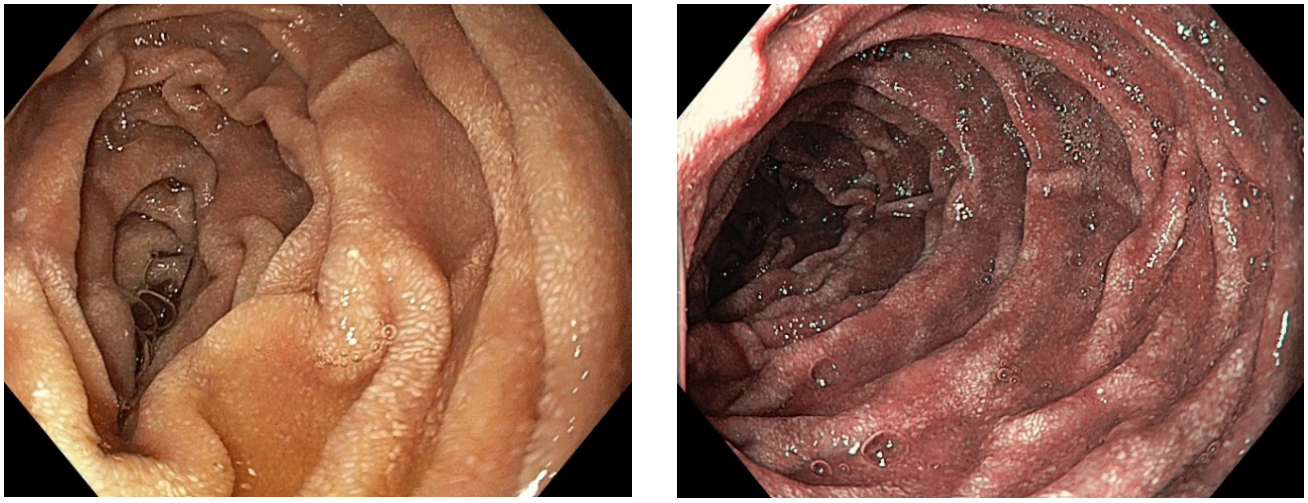

**Figure 1.** Slightly enlarged villi with an accumulation of whitish matter at the tip of the villi of duodenal mucosa.

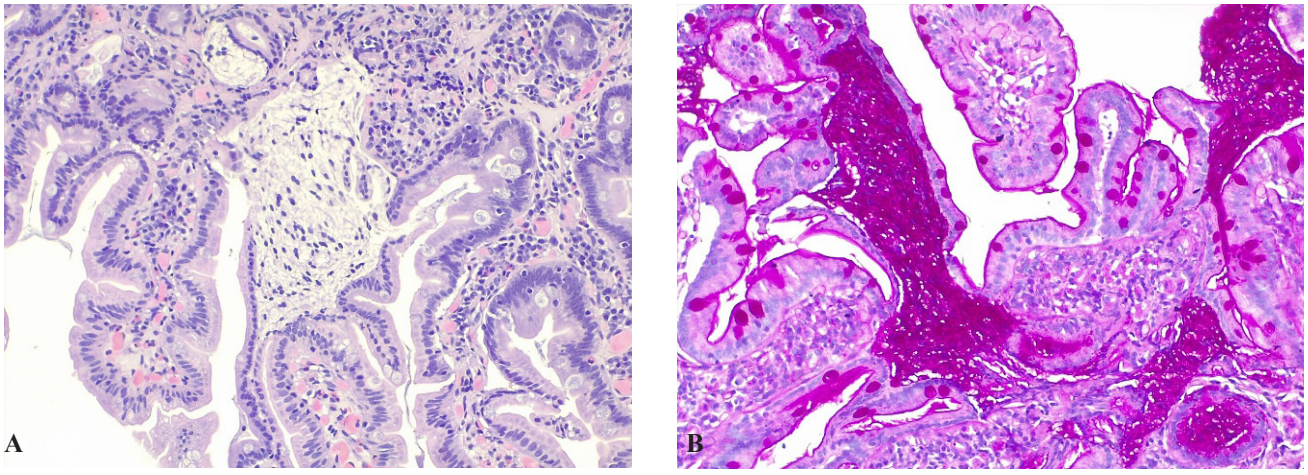


**Figure 2. A.** Duodenal mucosa with lympho-plasmocytes infiltrate and mucinous material in lamina propria (hematoxylin-eosin stain, x40); **B.** PAS-positive inclusions.

## Discussion

WD is a systemic chronic infectious disease first described by George Whipple in 1907. Dr. Whipple considered the observed intestinal lipodystrophy to be the result of a disturbed lipid metabolism, not an infection. Bacterial etiology was suspected in 1952, when the first treatment with antibiotics appeared to be successful. However, only in 1992, the bacteria was identified by molecular methods. It received the name of Tropheryma whippelii and in 2001 it was renamed according to the correct spelling - Tropheryma whipplei [1,7].

WD disease is a rare disorder with the most cases reported in North America and Europe. The incidence rate is 1-3 cases per 1 000 000 people, mean age of symptoms onset is 55 years. The disease is predominantly more common for male population, with male/female ratio: 8-4 to 1. WD is associated with the HLA B27 haplotype [8,9].

The name of this bacterium – *Tropheryma* - is derived from Greek "trophe" (nourishment) and "eryma" (barrier) because of the resulting intestinal affectation. It is Gram-positive bacillus, periodic acid-Schiff-positive (PAS-positive) and acid-fast negative. Bacillus core is enclosed within a plasma membrane, which is surrounded by a three layered cell wall. The inner layer contains polysaccharides that stain positive with PAS. This feature is used for histological diagnosis [10].

Detailed pathogenesis of WD remains unclear, but it

is clear that the host immunity plays an important role. Most individuals who contract T. whipplei are asymptomatic carriers or develop protective immunity after a limited intestinal infection. Only a small proportion develop chronic disease and that is, probably, due to abnormal, insufficient immune response. It consists primarily of altered macrophage function and an impaired type 1 T-cell response. These mechanisms lead to intestinal damage and the spread of bacteria with systemic affectation [6,10].

The most common symptoms of Whipple's disease are weight loss, diarrhea, and arthropathy. These symptoms may occur simultaneously, while arthropathy may precede gastrointestinal symptoms for many years. Systemic symptoms, such as low-grade intermittent fever, night sweats, and lymphadenopathy are quite frequent in Whipple's disease. Other, less frequent symptoms may include pulmonary, cardiac, muscle and central nervous system involvement [1,7,11].

As Whipple's disease is uncommon and since the same clinical manifestations may be observed in other diseases as well, therefore laboratory confirmation is compulsory. Current diagnostic criteria require positive results for PAS-positive foamy macrophages in the small bowel biopsy. The diagnosis can be also established through PAS-positive foamy macrophages in a biopsy specimen of the involved tissues. Molecular methods, like PCR detection of T. whipplei or detection of the specific 16S ribosomal RNA of the bacterium have high sensitivity, but may be false-positive. A more specific method is immunohistochemical staining with T. whipplei antibodies [6,7,10].

Returning to our case, we consulted our biopsy at the Synevo laboratory in Bucharest and received the same result. In this specific case, a positive histological diagnosis is not supported by clinical manifestations, neither intestinal nor extra-intestinal. Furthermore, there are no laboratory signs of malabsorption or of general inflammatory syndrome. Molecular methods are not available.

A passive observation tactic was chosen because of patient's good general condition and absence of strong evidence of WD. Control upper endoscopy in November 2020 demonstrated a positive evolution with less accumulation of whitish matter in the upper part of the villi. At the moment, there are no clinical manifestations or laboratory signs of disease.

There are two possible explanations for this clinical case. PAS-positive inclusions cannot only be in Tropheryma whipplei infection, but may be associated with another intestinal microbial or mycotic infection, which could lead to false positive histological result. This situation is more typical for immunosuppressive patients or in the case of HIV infection, but we can also assume that long-term treatment with PPIs may contribute to intestinal infection with other, possibly commensal microorganisms. Or, a more serious but less likely explanation: it is a case of the slow, silent evolution of Whipple's disease. Further clinical observation and repeat histological examination may be useful for diagnosis.

## Conclusion

It is still a difficult medical task to diagnose Whipple's disease. Histological findings may confirm the diagnosis in patients with a combination of typical manifestations such as fever, weight loss, arthropathy and diarrhea. However, typical histological signs alone are not pathognomonic, and are not enough for a definitive diagnosis. It may take several years from the initial examination until the diagnosis of WD.

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